PCT/EP2004/006814

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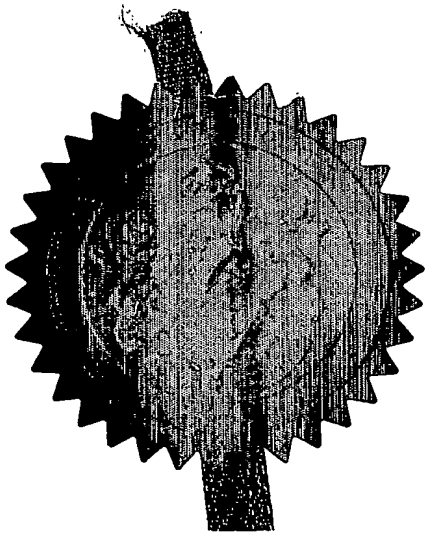

Signed Stephen Hordley

Dated 17 May 2004

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25JUN03 E817574-1 D02029
P01/7700 0.00-0314738.6

Request for grant of a patent

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The Patent Office
Cardiff Road
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Gwent NP9 1RH

1. Your reference — MA/LTH/PB60330P

2. Patent application number
(The Patent Office will fill in his part) — 0314738.6 — 24 JUN 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)* 4735870003

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)*

Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent
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GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* 8072555004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
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c) any named applicant is a corporate body
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Patents Form 1/77

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Continuation sheets of this form	17
Description	3 CF
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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature [signature] Date 24-Jun-03

M Atkinson

12. Name and daytime telephone number of person to contact in the United Kingdom: M Atkinson 01279 631323

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PB60330P

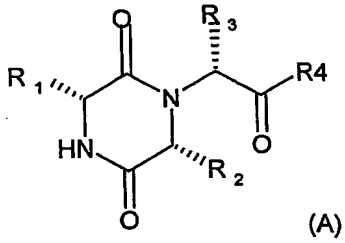
NOVEL COMPOUNDS

This invention relates to novel diketopiperazine derivatives having a potent and selective antagonist action at the oxytocin receptor, to processes for their preparation, pharmaceutical compositions containing them and to their use in medicine.

The hormone oxytocin is potent contractor of the uterus and is used for the induction or augmentation of labour. Also the density of uterine oxytocin receptors increases significantly by >100 fold during pregnancy and peaks in labour (pre-term and term).

Pre-term births/labour (between 24 and 37 weeks) causes about 60% of infant mortality/morbidity and thus a compound which inhibits the uterine actions of oxytocin e.g. oxytocin antagonists, should be useful for the prevention or control of pre-term labour.

International patent application PCT/EP02/14823 describes a class of diketopiperazine derivatives which exhibit a particularly useful level of activity as selective antagonists at the oxytocin receptor. A preferred class of compounds described therein is represented by the formula A

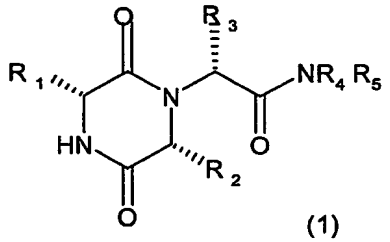


(A)

Such compounds include those wherein inter alia R_1 is 2-indanyl, R_2 is C_{3-4}alkyl, R_3 is a 5 or 6 membered heteroaryl group linked to the rest of the molecule via a carbon atom in the ring, R_4 represents the group NR_5R_6 wherein R_5 and R_6 each represent alkyl e.g. methyl or R_5 and R_6 together with the nitrogen atom to which they are attached form a 3 to 7 membered saturated heterocyclic ring which heterocycle may contain an additional heteroatom selected from oxygen.

We have now found a novel group of selective oxytocin receptor antagonists which exhibit a particularly advantageous pharmacokinetic profile.

The present invention thus provides compounds of formula (1)



(1)

Wherein R_1 is 2-indanyl, R_2 is 1-methylpropyl, R_3 is 2-methyl-1,3-oxazol-4-yl and R_4 and R_5 each represent methyl or R_4 and R_5 together with the nitrogen atom to which they are attached represents a pyrrolidino, morpholino, azetidino, 3-hydroxyazetidino, 3-methoxyazetidino or 3-fluoroazetidino and physiologically acceptable salts thereof.

The group R_2 contains an asymmetric carbon atom and the invention includes each enantiomer and mixtures thereof including the racemate.

A preferred group of compounds of formula (1) are those wherein R_4 and R_5 each represent methyl or R_4 and R_5 together with the nitrogen atom to which they are attached represent a morpholino group. Particularly preferred compounds of the invention include those, the preparation of which are specifically described in the examples

The compounds of formula (I) have a high affinity for the oxytocin receptors on the uterus of rats and humans and this may be determined using conventional procedure. For example the affinity for the oxytocin receptors on the rat uterus may be determined by the procedure of Pettibone et al, Drug Development Research 30. 129-142 (1993). The compounds of the invention also exhibit high affinity at the human recombinant oxytocin receptor in CHO cells and this may be conveniently demonstrated using the procedure described by Wyatt et al. Bioorganic & Medicinal Chemistry Letters, 2001 (11) p1301-1305.

The compounds of the invention are therefore useful in the treatment or prevention of diseases and/or conditions mediated through the action of oxytocin. Examples of such diseases and/or conditions include pre-term labour, dysmenorrhea, endometriosis and benign prostatic hyperplasia.

The compounds may also be useful to delay labour prior to elective caesarean section or transfer of the patient to a tertiary care centre. The compounds of the invention may also be useful for improving fertility rates in animals, e.g. farm animals.

The invention therefore provides for the use of a compound of formula (I) and/or physiologically acceptable salts for use in therapy and in particular use as medicine for antagonising the effects of oxytocin upon the oxytocin receptor.

The invention also provides for the use of a compound of formula (I) and/or a physiologically acceptable salt thereof for the manufacture of a medicament for antagonising the effects of oxytocin on the oxytocin receptor.

According to a further aspect, the invention also provides for a method for antagonising the effects of oxytocin upon the oxytocin receptor, comprising administering to a patient in need thereof an antagonistic amount of a compound of formula (I) and/or a physiologically acceptable salt thereof.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylactics as well as the treatment of established diseases or symptoms.

It will further be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated, the route of administration and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician. In general however doses employed for adult human treatment will typically be in the range of 2 to 800mg per day, dependent upon the route of administration.

Thus for parenteral administration a daily dose will typically be in the range 2 to 50mg, preferably 5 to 25mg per day. For oral administration a daily dose will typically be within the range 10 to 800mg, e.g. 20 to 150 mg per day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt or non-toxic metabolically labile esters thereof together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compositions of the invention include those in a form especially formulated for oral, buccal, parenteral, inhalation or insufflation, implant or rectal administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or

polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; solubilizers such as surfactants for example polysorbates or other agents such as cyclodextrins; and preservatives, for example, methyl or propyl p-hydroxybenzoates or ascorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

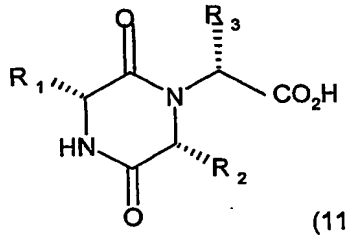
For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

The compositions according to the invention may contain between 0.1-99% of the active ingredient, conveniently from 30-95% for tablets and capsules and 3-50% for liquid preparations.

The advantageous pharmacokinetic profile of the compounds of the invention is readily demonstrated using conventional procedures for measuring the pharmacokinetic properties of biologically active compounds.

Compounds of formula (1) may be prepared by reaction of the carboxylic acid (11, wherein R_1, R_2 and R_3 have the meanings defined in formula 1).

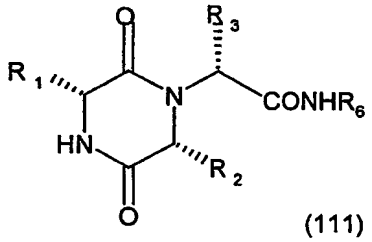


(11)

or an activated derivative thereof with the amine NHR_4R_5 wherein R_4 and R_5 have the meaning defined in formula (1) under standard conditions for preparing amides from a carboxylic acid and an amine HNR_4R_5.

Thus the amides may be prepared by treating the carboxylic acid of formula (11) with an activating agent such as BOP (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate),TBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate), BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride) or oxalyl chloride in an aprotic solvent such as dichloromethane optionally in the presence of a tertiary amine such as triethylamine and subsequent reaction of the product thus formed with the amine NHR_4R_5.

Alternatively, compounds of formula (1) may be prepared by reacting a compound of formula (111)



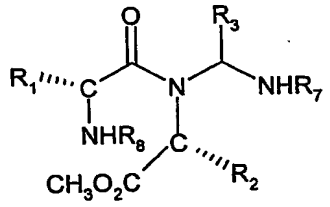
(111)

(wherein R_1R_2 and R_3 have the meanings defined in formula (1) and R_6 is 2-hydroxy phenyl) with carbonyl dimidazole or thiocarbonyl diimidazole in a suitable solvent such as dichloromethane and subsequent reaction of the products this formed with the amine HNR_4R_5.

Compounds of formula (11) may be prepared from a compound of formula (111) wherein R_6 is 2-hydroxyphenyl by reaction with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent such as dichloromethane and subsequent reaction of the product thus formed with aqueous acetone.

Compounds of formula (111) wherein R_6 is 2-hydroxphenyl may be from the corresponding compounds of formula (111) wherein R_6 is a 2-benyloxyphenyl group by hydrogenolysis using hydrogen and a palladium catalyst.

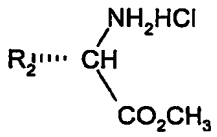
Compounds of formula (111) wherein R_6 is a 2-benyloxyphenyl group are conveniently prepared by the process described herein below. Thus compounds of formula (III) may be prepared from the compound of formula (IV)



(IV)

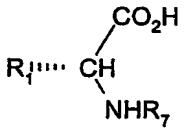
wherein R_1, R_2 and R_3 have the meanings defined in formula (I), R_7 is 2-benzyloxyphenyl and R_8 is N-benzyloxycarbonyl by the reaction with hydrogen in the presence of a palladium on charcoal catalyst and acetic acid. This reaction is conveniently carried out in a solvent such as ethanol or trifluoroethanol or mixtures thereof.

The compound of formula (IV) may be prepared by reacting the amino ester hydrochloride (V), wherein R_2 has the meaning defined and formula (I)



(VI)

with the aldehyde R_3CHO (VI) wherein R_3 has the meanings defined in formula (I), in the presence of triethylamine and in a solvent such as trifluoroethanol and then reacting of the resultant product with the compound (VII) wherein R_1 has the meanings defined in formula (I) and R_7 is a benzyloxycarbonyl



(VII)

and the isocyanide CNR_6 (VIII) wherein R_6 is a 2-benzyloxyphenyl group, in a solvent such as trifluorethanol.

The R_2 substituent is a 1-methylpropyl group and the compound of formula (I) wherein R_2 is a 1-methylpropyl group having an (S) or (R)

configuration may be prepared by starting with the aminoester (V) wherein the R_2 group has the required (S) or (R) configuration.

The following examples are illustrative, but not limiting of the embodiments of the present invention.

General purification and analytical methods

Analytical HPLC was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID), eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO_2H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 minutes 0%B, 0.7-4.2 minutes 0%-100%B, 4.2-5.3 minutes 100%B, 5.3-5.5 minutes 0%B at a flow rate of 3 ml/minute. The mass spectra (MS) were recorded on a Fisons VG Platform spectrometer using electrospray positive [(ES+ve to give MH^+ and $M(NH_4)^+$ molecular ions] or electrospray negative [(ES-ve to give $(M-H)^-$ molecular ion] modes on a Micromass series 2 or a Waters ZQ mass spectrometer. ^1H NMR spectra were recorded using a Bruker DPX 400MHz spectrometer using tetramethylsilane as the external standard. Biotage™ chromatography refers to purification carried out using equipment sold by Dyax Corporation (either the Flash 40i or Flash 150i) and cartridges pre-packed with KPSil. Mass directed autoprep refers to methods where the material was purified by high performance liquid chromatography on a HPLCABZ+ 5µm column (5cmx10mm i.d.) with 0.1% HCO_2H in water and 95% MeCN, 5% water

(0.5% HCO_2H) utilising gradient elution at a flow rate of 8ml $minutes^{-1}$. The Gilson 202-fraction collector was triggered by a VG Platform Mass Spectrometer on detecting the mass of interest.

Hydrophobic frits refer to filtration tubes sold by Whatman. SPE (solid phase extraction) refers to the use of cartridges sold by International Sorbent Technology Ltd. TLC (thin layer chromatography) refers to the use of TLC plates sold by Merck coated with silica gel 60 F_{254}. Oasis™ refers to Waters® Oasis™ HLB Extraction Cartridges, sold by Waters Corporation®.

Intermediate 1

2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-N-(2-hydroxyphenyl)-2-(2-methyl-1,3-oxazol-4-yl)acetamide

To a vigourously stirred solution of (D)-allo Isoleucine methyl ester hydrochloride (5.0g) in dichloromethane (150ml) was added a saturated sodium bicarbonate solution (150ml). The resultant bi-layer was separated using a hydrophobic frit and the aqueous phase washed twice with dichloromethane (50ml). The combined dichloromethane phase was diluted with methanol (200ml) and (2R)-[(benzyloxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (14.64g) added and the mixture vigorously stirred for 1hr to effect solution. The solution was evaporated and the residue dissolved in a mixture of 1:1 trifluoroethanol / methanol

(140ml), and then 2-benzyloxyphenylisocynanide (9.43g) was added followed by 2-methyl-4- formyloxazole(5.0g) and the reaction stirred for 4 days at room temperature. The mixture was evaporated and the residue dissolved in ethanol (500ml) and palladium on carbon (4.0g) and acetic acid (10ml) added and the reaction mixture was stirred under an atmosphere of hydrogen for 3 hours. Further fresh palladium on carbon (4.0g) and acetic acid (20ml) added and the reaction mixture was stirred under an atmosphere of hydrogen for a further 16 hours. The mixture was filtered through Celite, evaporated and the residue dissolved in ethyl acetate (300ml) washed with water (2x100ml), saturated sodium bicarbonate solution (2x100ml) and brine (100ml) and then passed through a hydrophobic frit and evaporated. The crude product was purified by column chromatography (silica) eluting with ethyl acetate(100% to 0%): methanol to give 2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-N-(2-hydroxyphenyl)-2-(2-methyl-1,3-oxazol-4-yl)acetamide (11.8 g 51%)

HPLC Rt = 3.2 minutes; m/z $[M+H]^+$ = 517.

Similarly prepared from (D)-isoleucine methyl ester hydrochloride

Intermediate 2

2-{(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-[(1*R*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-*N*-(2-hydroxyphenyl)-2-(2-methyl-1,3-oxazol-4-yl)acetamide

HPLC Rt = 3.17 and 3.22 minutes; m/z $[M+H]^+$ = 517.

Intermediate 3

{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}(2-methyl-1,3-oxazol-4-yl)acetic acid

Carbonyldiimidazole (352mg, 1.6 equiv.) was added to a solution of 2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-N-(2-hydroxyphenyl)-2-(2-methyl-1,3-oxazol-4-yl)acetamide (11.8 g pre-dried in vacuo over P_4O_{10} for 24 hours) in dichloromethane (20mL) and the solution was left at room temperature for 16 hr. The mixture was evaporated and the residue dissolved in acetone (20ml) and water (20ml) added, followed by addition of 2NHCl (2ml) and the mixture left at room temperature for 4.5 hr. This was extracted with ethylacetate (2x30ml) and the combined organic phase dried via a hydrophobic frit and evaporated. The residue was taken up in ethylacetate (30ml) washed with 2NHCl (2x10ml) and then extracted with saturated sodium bicarbonate solution (2x15ml). The combined aqueous phase was acidifed with 2NHCl and extracted with ethylacetate (2x20ml) and the combined organic phase washed with brine dried via a hydrophobic frit and evaporated to give {(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}(2-methyl-1,3-oxazol-4-yl)acetic acid (0,355mg, 73%) as a white solid.

HPLC Rt = 3.0 and 3.1 minutes; m/z $[M+H]^+$ = 426

Similarly prepared from intermediate 2

{(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-[(1*R*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}(2-methyl-1,3-oxazol-4-yl)acetic acid (Intermediate 4)

HPLC Rt = 3.14 minutes; m/z $[M+H]^+$ = 426

Example 1

(2R)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-N,N-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide

Diisopropylamine (100mg 3.3equiv.), pyBOP (159mg, 1.3equiv.) and a 1M solution of dimethylamine in tetrahydrofuran (1.175ml, 5 equiv.) were added sequentially to a solution of {(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}(2-methyl-1,3-oxazol-4-yl)acetic acid (100mg) in dimethylformamide (2ml) and the mixture stirred for 4 days at room temperature. The reaction was diluted with dichloromethane (10ml) and 2NHCl (10ml) added. The organic phase was separated, washed with saturated sodium bicarbonate solution (10ml) dried via a frit and evaporated. The residue was purified by preparative HPLC to give (2R)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-N,N-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide (27mg, 25%) as a colourless solid.

HPLC Rt = 2.9 minutes; m/z $[M+H]^+$ = 453

^1H NMR ($CDCl_3$) □ 7.72 (s, 1H), 7.26-7.15 (m, 4H), 6.29 (s, 1H), 4.18 (d, 1H), 4.07 (d, 1H), 3.18-3.11 (m, 3H), 3.00 (d, 6H), 2.95-2.85 (m, 1H), 2.82-

2.75 (m, 1H), 2.49 (s, 3H), 1.66-1.58 (m, 1H), 1.52-1.43 (m, 1H), 1.05-0.95 (m, 1H), 0.82-0.73 (m, 6H)

Similarly prepared from intermediate 3 and morpholine:

Example 2

(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1S)-1-methylpropyl]-2,5-piperazinedione colourless solid, 22%

HPLC Rt = 2.8 minutes; m/z $[M+H]^+$ = 495

^1H NMR ($CDCl_3$) □ 7.72 (s, 1H), 7.26-7.15 (m, 4H), 6.93 (d, 1H), 6.30 (s, 1H), 4.18 (d, 1H), 4.06 (dd, 1H), 3.70-3.30 (m, 8H), 3.17-3.10 (m, 3H), 2.98-2.86 (m, 1H), 2.81-2.75 (m, 1H), 2.49 (s, 3H), 1.69-1.60 (m, 1H), 1.50-1.43 (m, 1H), 1.05-0.95 (m, 1H), 0.80-0.75 (m, 6H).

Similarly was prepared from intermediate 4 and morpholine

Example 3

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1*R*)-1-(2-methyl-1,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1*R*)-1-methylpropyl]-2,5-piperazinedione

HPLC Rt = 2.92 minutes; m/z $[M+H]^+$ = 495

Similarly prepared from intermediate 4 and dimethylamine

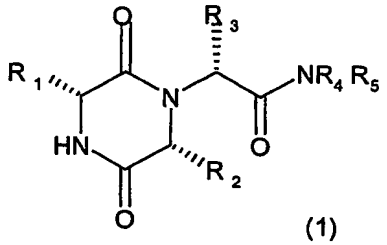
Example 4

(2*R*)-2-{(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-[(1*R*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-*N*,*N*-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide

HPLC Rt = 2.83 minutes; m/z [M+H]+ = 453

Claims

1. A compound of formula (1)



(1)

wherein R_1 is 2-indanyl, R_2 is 1-methylpropyl, R_3 is 2-methyl-1,3-oxazol-4-yl and R_4 and R_5 each represent methyl or R_4 and R_5 together with the nitrogen atom to which they are attached represents a pyrrolidino, morpholino,azetidino, 3-hydroxyazetidino, 3-methoxyazetidino or 3-fluoroazetidino group and physiologically acceptable salts thereof.

2. A compound as claimed in claim 1 wherein R_4 and R_5 each represent. methyl or R_4 and R_5 together with the nitrogen atom to which they are attached represent a morpholino group.

3. (2R)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-N,N-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide 4 (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1S)-1-methylpropyl]-2,5-piperazinedione.

4. A compound selected from :-

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1*R*)-1-(2-methyl-1,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1*R*)-1-methylpropyl]-2,5-piperazinedione;

(2*R*)-2-{(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-[(1*R*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-*N*,*N*-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide.

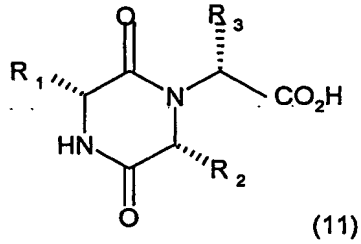
5. A pharmaceutical composition comprising a compound of formula (1) as claimed in 1 together with one or more pharmaceutically acceptable carriers.

6. The use of compound of formula (1) as defined in claim 1 for the manufacture of a medicament for antagonising the effects of oxytocin on the oxytocin receptor.

7. A method of treating or preventing diseases or conditions mediated through the action of oxytocin which comprises administering to a mammal in need thereof of an effective amount of a compound of the formula (I)

8. A process for A the preparation of compounds of formula (I) which comprises:

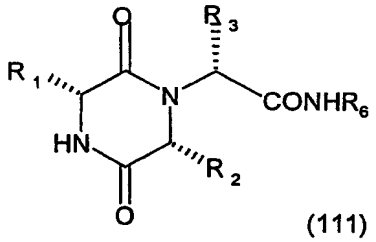
(a) reacting a compound of formula (II)



(11)

wherein R_1, R_2 and R_3 have the meanings defined in claim 1 with the amine NHR_4R_5 wherein R_4 and R_5 have the meaning defined in formula (I) under the standard condition for preparing amides from a carboxylic acid and an amine.

(b) reacting a compound of formula (III)

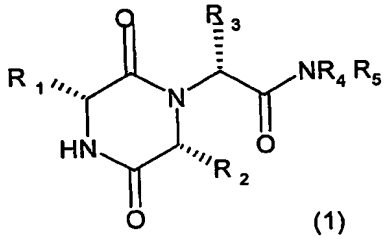


(111)

wherein R_1, R_2 and R_3 have the meanings defined in claim 1 and R_6 is 2-hydroxyphenyl with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent and subsequent reaction of the product thus formed with amine NHR_4R_5 wherein R_4 and R_5 have the meaning defined in formula (I).

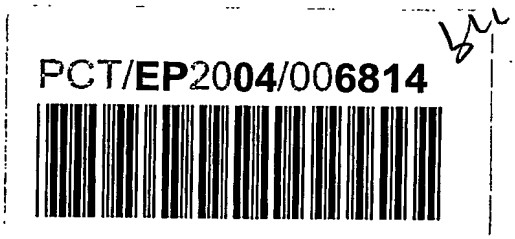
ABSTRACT

Compounds of formula (1)



(1)

Wherein R_1 is 2-indanyl, R_2 is 1-methylpropyl, R_3 is 2-methyl-1,3-oxazol-4-yl and R_4 and R_5 each represent methyl or R_4 and R_5 together with the nitrogen atom to which they are attached represents a pyrrolidino, morpholino, azetidino, 3-hydroxyazetidino, 3-methoxyazetidino or 3-fluoroazetidino, process for their preparation, pharmaceutical compositions containing them and their use in medicine.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